### Title

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# Brain metastases in osteosarcoma: incidence, clinical and neuroradiological findings and management options

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*Key words:* osteosarcoma, brain, metastases, presentation, neuroradiology

**Summary**

Brain metastasis is uncommon in osteosarcoma, but this may be changing with prolonged patient survival in the modern chemotherapy era. We present 5 patients with brain metastases out of 39 with lung metastasis (13%) in a total of 87 osteosarcoma patients.

The clinical manifestations of brain metastases were catastrophic: massive hemorrhage in 2 and status epilepticus in 3. Metastases were single or multiple, and some were osteoblastic. Surgical intervention in 2 cases resulted in dramatic, though transient, clinical improvement.

We advocate periodic neuroradiology screening in osteosarcoma patients with lung metastases, for early detection of brain involvement.

## Introduction

Osteosarcoma, one of the most common malignant bone tumors in children and adolescents, rarely metastasizes to the central nervous system. The pattern of dissemination of this neoplasm is usually hematogenous, with lungs and bone being the main targets [1–8]. Thus, in a large series of patients with osteosarcoma, 90% of those who relapsed had lung metastases and approximately 50% had bone lesions [3]. Brain metastases were usually found only in autopsy series or as a late, pre-terminal event [3, 5, 8].

The initiation of chemotherapy for osteosarcoma in the early 70's has altered the natural history of this disease [6–10]. While lung metastases would generally appear within the first year, and the five-year survival was less than 20% in pre-chemotherapy days, current results are far superior, yielding survival rates in excess of 60% [1, 2]. Moreover, the prolonged survival of patients has permitted the appearance of new, significant targets for metastasis, such as the heart, abdomen and brain [7–10]. In the past year, we have observed the occurrence of brain metastases in several children and adolescents with osteosarcoma. This prompted a review of the records of all patients with this neoplasm seen and treated at our institution in the past 5 years. This report summarizes the incidence, clinical presentation, management, and outcome of these patients.

## Patients and methods

### *Patients*

Consecutive untreated pediatrc patients with osteosarcoma, admitted from 1980 to 1986 to the M. D. Anderson Hospital were evaluated. They were initially randomized to two preoperative chemotherapy regimens: high dose methotrexate with citrovorum factor (MTS-CF) and intra-arterial cis-diamminedichloroplatinum II (CDP). The initial

treatment was administered for 6 to 12 weeks, provided a response was achieved. Thereafter, a surgical procedure was performed. The extent of tumor destruction was then assessed by pathologic examination of the surgical specimen. Patients responding to the preoperative treatment (over 60% destruction) continued with the agent used preoperatively and with the addition of other agents (Fig. 1). Alternatively, if preoperative treatment was considered ineffective (tumor destruction under 60%), the preoperative agent was discarded. The total duration of postoperative adjuvant treatment was one year.

Prior to the initiation and during the course of treatment, routine chest radiographs were obtained at monthly intervals and computerized tomography (CT) scans of the chest and bone scans at 6 monthly intervals. Other investigations were obtained as dictated by the clinical status. Finding of pulmonary metastases led to surgical consultation and, when feasible, resection of the metastases. In all cases, the diagnosis of osteosarcoma was confirmed by pathologic examination of the presenting tumor. Eighty seven patients were considered evaluable for review, including two admitted with pulmonary metastases.

## Results

Table 1 illustrates the patient characteristics of this patient population. Comparison of age, sex, and time-to-pulmonary-metastasis revealed no difference between the total patient population and those who developed brain metastases. All patients with brain metastases had developed pulmonary disease, some of which were resected. In all cases, the appearance of brain metastases was concurrent with, or subsequent to, occurrence of lung metastases. Table 2 illustrates the salient features of the 5 patients with brain metastases. The CT in 2 cases revealed a hemorrhagic mass lesion (Fig. 2), surgically verified in 1 case. Dense calcification and/or osteoid was seen in the lesions of 1 patient (Fig. 3), which was confirmed pathologically. The CT scans of 2 patients were performed at outside hospitals and were unavailable for review by us, but reportedly were consistent with brain metastasis in both cases (no autopsies were done). At the time of diagnosis of metastatic brain disease, 3 of the 5 patients presented with seizures, progressing to status epilepticus in 2 cases. One patient presented with rapid deterioration of mental status, accompanied by vomiting and signs of uncal herniation secondary to a massive

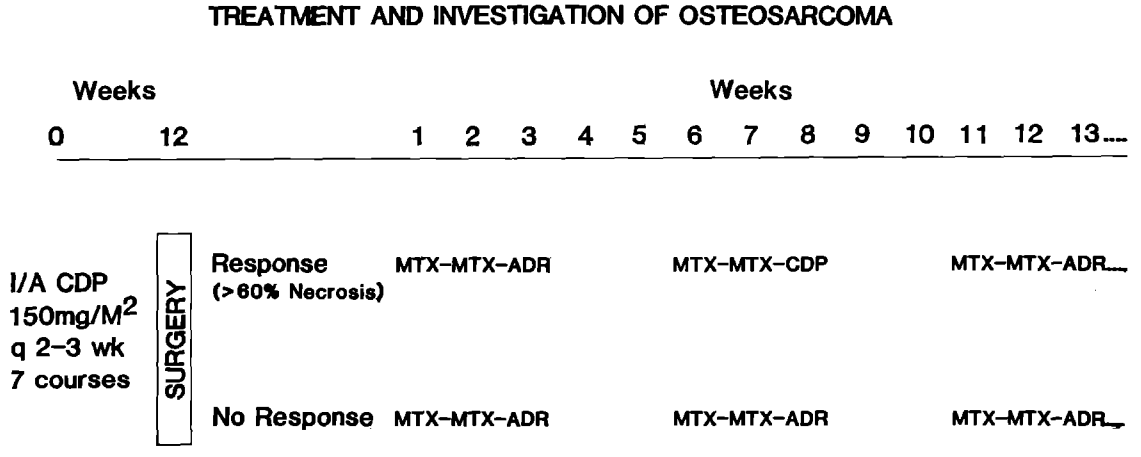



*Fig. 1.* TIOS (Treatment and Investigation of Osteosarcoma). Patients were assigned to receive 7 courses (12 weeks) of intra-arterial cis-diamminedichloroplatinum-II (CDP) as induction therapy, followed by a surgical procedure. The extent of tumor destruction was assessed. Patients responding to the preoperative treatment (over 60% tumor necrosis) continued treatment with the agent utilized preoperatively with the addition of other agents. Alternatively, if tumor destruction was under 60%, the preoperative agent was discarded. The total duration of postoperative adjuvant therapy was one year. MTX = High dose methotrexate (12.5 gm/$M^2$) with citrovorum factor rescue (15–100 mg q3h IV). ADR = Adriamycin 25 mg/$M^2$/dx3.

*Table 1.* Characteristics of patients with osteosarcoma (n = 87).

| | |
|---|---|
| Mean age at diagnosis: | 11.8 years (range 1 – 16 years) |
| Sex: | Males:Females 40:48 (46%:54%) |
| Follow-up time: | < 1 – 6 years (mean 2.4) |
| Survival: | 55 alive; 32 dead; 1 unknown |
| Patients with pulmonary metastases: | n = 39 |
| Time to pulmonary metastases: | mean = 13, range: diagnosis – 48 months |
| Survival in patients with pulmonary metastases: | 12 alive; 27 dead; 1 unknown |

*Table 2.* Characteristics of patients with osteosarcoma metastatic to brain.

| Patient | Age[a]/Sex | Pathology | Time to pulmonary metastasis | Interval to brain metastasis | Presentation | Location of metastasis |
|---|---|---|---|---|---|---|
| 1 | 15/M | chondroblastic | 9 mo | 46 mo | focal-generalized seizures | L parietal, hemorrhagic R occipital × 2 |
| 2 | 11/F | chondroblastic | 45 mo | < 2 mo | status epilepticus | CT unavailable[b] |
| 3 | 12/M | osteoblastic | 15 mo | 12 mo | asymptomatic | CT unavailable[b] |
| 4 | 8/F | osteoblastic | 22 mo | 17 mo | status epilepticus | R frontal lobe |
| 5 | 14/F | small cell | 1 wk | 9 mo | rapidly declining mental status | L frontal lobe, hemorrhagic |

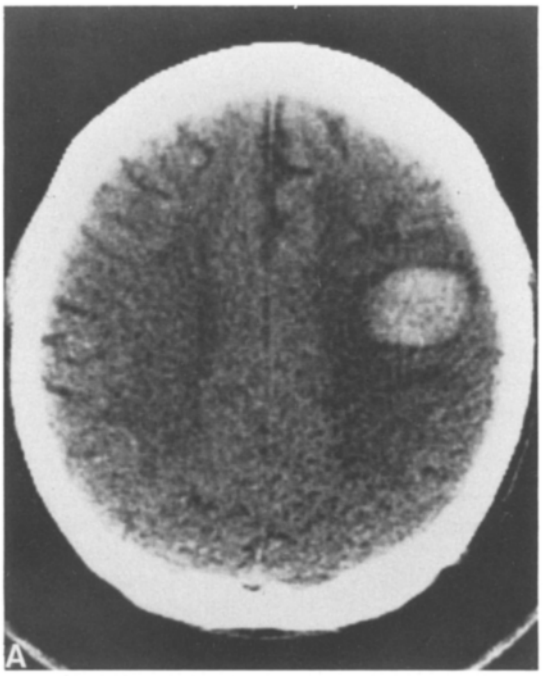
[a]At diagnosis; [b]Performed at outside hospitals, exact location of metastases not reported.

hemorrhage (metastasis verified by surgical specimen). The fifth patient was found to have cranial involvement on routine skeletal survey, and a subsequent CT confirmed parenchymal brain involvement. In patients 2 and 3 (Table 2) neuroradiological studies were performed at an outside hospital and information about exact metastasis localization was unavailable. The gross surgical resection of the intracranial metastases in 2 cases led to clinical improvement for several months. The outcome in all 5 patients, however, has been uniformly fatal.

## Discussion

The prognosis and survival in osteosarcoma have been dismal until the past two decades [1, 2, 6, 10]. Despite surgical extirpation of the tumor, most patients relapsed in lungs, and preterminally had disseminated disease [3 – 5, 8]. Major advances have been made in the past decade and a half in eradicating the primary disease and arresting its dissemination [1, 2, 6, 8]. There are few reports on brain metastases from osteosarcoma. Most were reported during the prechemotherapy era. Dahlin *et al.* [5] reported 3 cases in an autopsy series of 150 patients. More recently, Danzinger *et al.* [11] presented 3 other patients with osteogenic sarcoma metastatic to the brain. Each of these patients had lung metastases before discovery of their brain lesions. The cerebral metastases were osteo-blastic in 2 of the 3 cases, diagnosed by skull roentgenography in one and CT in the other. The lesions were hypervascular at angiography in 2 cases. One of the patients presented with a focal seizure, the second with progressive hemiparesis, and the third was asymptomatic. There was no information in this report as to the incidence or prevalence of brain metastases from osteogenic sarcoma. Giuliano *et al.* [8] also mentioned two patients with brain metastases among their 111 patients, but provided no further details.

It is unclear whether patients whose pulmonary metastases have been eliminated by surgery or chemotherapy remain at a high risk for brain lesions. A slow subclinical growth of a brain metastasis, established at the time of presence of the lung lesion,



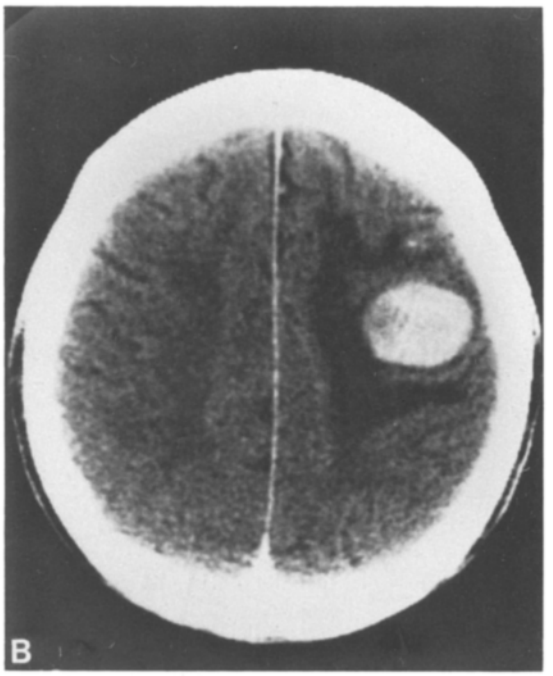





*Fig. 2.* Pre (A) and postcontrast (B) scans of patient 1 demonstrate a hemorrhagic, enhancing lesion in the left frontoparietal region with associated edema. (C) Noncontrast scan of patient 5 shows a large left frontal hemorrhage with mass effect. At surgery, there was an underlying osteosarcoma metastasis.

or possible persistence of micrometastases in the lung may underlie a "late" appearance of a brain lesion on CT. Notwithstanding, it would seem that clinical detection of brain metastases (as opposed to findings on autopsy) can be attributed to the prolonged survival and change in metastatic patterns induced by chemotherapy [1, 2, 6, 8].

The 87 patients in the present report were treated with a uniform protocol and had a 45% incidence of pulmonary metastases. Patients with this complication, in turn, had a 13% incidence of brain metastases. There was no predilection of any particular age or pathological variant of osteosarcoma for the development of this complication. The clinical presentation has tended to be acute and catastrophic, necessitating emergency management and accompanied by major morbidity. Solitary metastases presenting in an otherwise stable individual with controlled peripheral disease could be amenable to surgical extirpation. Since early detection may avert some of the catastrophic complications of brain metastasis, we recommend routine, periodic screening (CT or magnetic resonance imaging) of the brain be undertaken in osteosarcoma patients with lung metastases.




*Fig. 3.* A and B. Precontrast scan with brain and bone settings in patient 4 show a lesion with bone formation and surrounding edema in the right frontal lobe. C. Postcontrast scan reveals mild peripheral enhancement. This lesion was surgically verified as osteosarcoma.

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